BILE ACID COMPOSITION MODULATES INSULIN RESISTANCE IN NON-DIABETIC PATIENTS WITH NAFLD

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EPoS Elucidating Pathways of Steatohepatitis

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INTRODUCTION

Bile acids (BAs) are signaling molecules synthesized in the liver from cholesterol through the formation of a common intermediate. The main primary BAs are cholic acid (CA) and chenodeoxycholic acid (CDCA).

In the liver, most of the BAs are conjugated with amino acids glycine or taurine to form conjugated primary BAs: G-CA, G-CDCA, T-CA, T-CDCA

At physiological pH BAs ionize and form salts that reach the gallbladder where they remain concentrated during fasting. After a meal, BAs are released in the duodenum where promote solubilization, digestion and absorption of dietary lipids.

In the intestine, primary BAs are modified by gut microflora through a series of biochemical modification leading to the formation of secondary BAs, mainly deoxycholic acid (DCA), litocholic acid (LC) and ursodeoxycholic acid (UDCA). Trough the enterohepatic circulation, most of BAs go up to the liver restoring the whole pool of Bas.

There is growing interest in the role of BAs in the pathogenesis of NAFLD because they can modulate both glucose and lipid metabolism in insulin resistance (IR), the main pathogenic mechanism involved in the progression to steatohepatitis (NASH)

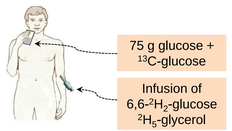
AIM

Since the association between BAs and insulin sensitivity (IS)/IR has not investigated at all in NAFLD, we aimed to assess the relationship between BAs composition and sites and mechanisms of IR in a well characterized biopsy proven NAFLD patients without diabetes.

METHODS

We studied 42 non-diabetic patients with biopsy proven NAFLD

Figure 1



- tracers studies coupled with a double-tracer Oral Glucose Tolerance Test (OGTT) to investigate glucose and lipid metabolism (Figure 1)

- Plasma BAs composition (university of Sidney, Australia)
- Tracers measurement (CNR, Pisa)

→ GC-MS

- **Hepatic-IR** (Hep-IR) was calculated as the product (Endogenous Glucose Production x fasting insulin)
- **Peripheral-IR** was derived from glucose clearance (GC) (glucose rate of disappearance/plasma glucose concentration)
- **Adipose tissue-IR** (AT-IR) was calculated as the product (glycerol Rate of appearance x fasting insulin)

RESULTS

Clinical and biochemical characteristics of the study cohort are reported in Table 1.

Table 1

Variables	N = 42
Age, y	43.2 11.5
BMI, kg/m^2	27.5 3.8
Waist, cm	96.2 10.2
AST, IU/l	33 (30-37)
ALT, IU/l	68 (44-76)
GGT, IU/l	59 (38-81)
Fasting glucose, mg/dl	97 (90-99)
Fasting insulin, mU/l	10.7 (9.6-12.9)
C-peptide, pmol/ml	1.0 0.35
Triglycerides, mg/dl	80 (75-100)
Total cholesterol, mg/dl	204 (187-212)
HDL-cholesterol, mg/dl	48 (44-52)

As shown in Table 2, more than half of the patients had advanced/severe fibrosis. Most of them had lobular inflammation and ballooning and the diagnosis of NASH was done in about 70% of cases.

Table 2

Fibrosis	
F0/F1	19 (45%)
F2	11 (26%)
F3/F4	12 (29%)
Lobular inflammation	
0	10 (24%)
1/2	32 (76%)
Ballooning	
0	5 (11%)
1	17 (41%)
2	20 (48%)
Steatosis (%)	38 (range 5-95)
NASH	28 (67%)

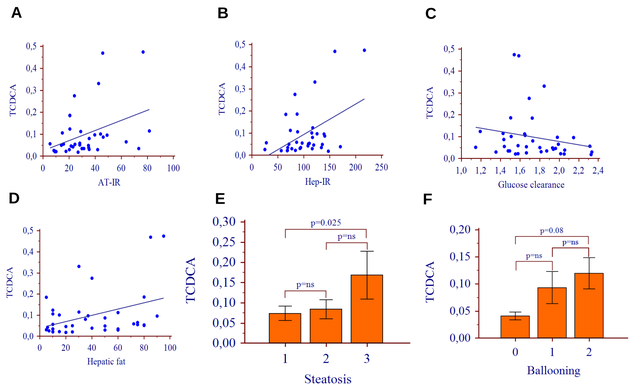
Among primary BAs, conjugated forms showed the best correlations with metabolic parameters (visceral adiposity by waist circumference, insulin secretion by C-peptide, Adipo-IR and Hep-IR) (Table 3).

Table 3

		Waist	C-peptide	Adipo-IR	Hep-IR	Per-IR
Primary BAs						
CA	rs	0,22	0,23	0,06	0,18	-0,04
	p	0,183	0,158	0,706	0,278	0,794
CDCA	rs	0,20	0,23	0,00	0,21	-0,07
	p	0,225	0,149	0,979	0,197	0,673
Primary conjugated BAs						
GCA	rs	0,38	0,46	0,40	0,38	-0,27
	p	**0,016**	**0,003**	**0,011**	**0,019**	0,098
GCDCA	rs	0,40	0,38	0,40	0,34	-0,30
	p	**0,010**	**0,017**	**0,011**	**0,035**	0,063
TCDCA	rs	0,38	0,56	0,47	0,40	-0,33
	p	**0,017**	**0,000**	**0,003**	**0,012**	**0,037**

Among primary conjugate BAs, T-CDCA showed the best correlations with metabolic parameters (Fig.1). T-CDCA significantly correlated with both AT-IR and Hep-IR (A-B), was inversly related to glucose clearance (C) and increased with hepatic fat (D-E) as well as with ballooning (F).

Figure 2



Curiously, Secondary Bas did not show any correlations with IR components suggesting that gut microflora did not negatively influence BAs composition (Table 4).

Table 4

Secondary BAs		Waist	C-peptide	Adipo-IR	Hep-IR	Per-IR
LC	rs	0,23	0,32	0,22	0,21	-0,29
	p	0,147	0,041	0,170	0,218	0,074
DCA	rs	-0,19	-0,03	0,01	0,08	0,02
	p	0,231	0,866	0,968	0,647	0,907
UDCA	rs	0,21	0,13	0,13	0,37	-0,09
	p	0,203	0,408	0,433	0,022	0,578

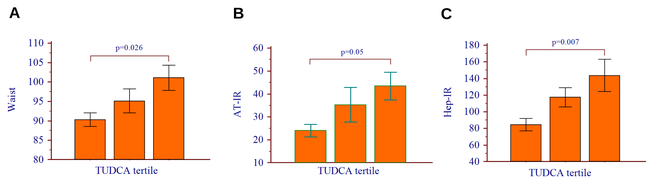
Similarly to primary conjugate BAs, secondary conjugated BAs showed the best correlation with metabolic parameters (Table 5).

Table 5

Secondary conjugated BAs		Waist	C-peptide	Adipo-IR	Hep-IR	Per-IR
GLC	rs	0,09	0,17	0,21	0,06	-0,22
	p	0,593	0,286	0,194	0,708	0,175
GDCA	rs	0,13	0,29	0,29	0,24	-0,21
	p	0,440	0,067	0,072	0,152	0,196
GUDCA	rs	0,32	0,26	0,32	0,44	-0,16
	p	0,042	0,100	0,043	0,005	0,333
TDCA	rs	0,12	0,33	0,26	0,18	-0,28
	p	0,470	0,038	0,103	0,276	0,082
TUDCA	rs	0,34	0,40	0,40	0,53	-0,17
	p	**0,033**	**0,010**	**0,011**	**0,001**	0,285

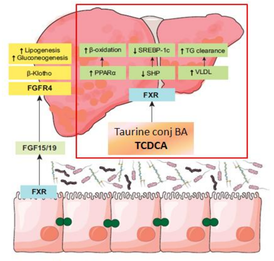
Now again, taurine conjugate UDCA (T-UDCA) showed the best correlations. Particularly, visceral obesity by waist circumference, AT-IR by lipolysis and Hep-IR by EGP levels increased proportionally with T-UDCA tertile (Figure 3 A-C).

Figure 3



CONCLUSIONS

- Among primary bile acids, the conjugated forms are proportionally increased to insulin resistance at the main sites of insulin action (adipose tissue and liver)
- Secondary bile acids, that reflect the action of the gut microflora, do not associate with metabolic parameters such as visceral obesity and insulin resistance
- Since taurochenodeoxycholic acid (T-CDCA) is the most potent endogenous agonist of FXR, we speculate that its increase may represent a compensatory mechanisms to reduce fat accumulation in the liver



Adapted from Marra F. and Svegliati-Baroni G. *J Hepatol* 2017

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